CN10-0614

International Research and Development Corporation

SPONSOR: Velsicol Chemical Company

COMPOUND: BP-4A

SUBJECT: Three Week Dermal Toxicity Study in Rabbits.

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163-549

TABLE OF CONTENTS

TABLE OF CONTENTS
(Continued)

I. SYNOPSIS

BP-4A was administered to the backs of New Zealand White rabbits, at dosage levels of 100, 500 and 2500 mg/kg/day, 5 days a week, for 3 weeks. Four male and four females rabbits were used at each dosage level and also in a control group. The control rabbits were administered 1.5 ml/kg of 0.9% physiological saline on the same regimen as treated rabbits. The compound was mixed with 0.9% physiological saline to form a paste which was applied. The rabbits were observed daily for signs of overt toxicity, dermal irritation, moribundity and mortality. Body weights were recorded weekly. Hematologic and biochemical studies and urinalyses were conducted during the pretest period and at 3 weeks of study.

There was no mortality and no sign of overt toxicity or unusual behavior for the rabbits in any group.

The application of BP-4A on the skin of rabbits at a dosage of 100 mg/kg/day occasionally elicited very slight erythema. The dosage of 500 and 2500 mg/kg/day evoked very slight erythema for almost all rabbits for varying lengths of time. There were no other signs of skin irritation or any signs of toxicity.

No changes considered to be related to compound were seen in body weights, hematologic and biochemical parameters and urinalysis.

There were no compound induced gross or microscopic lesions in any of the tissues examined. No compound-related organ weight variations occurred.

II. COMPOUND

The compound was received from Velsicol Chemical Corporation, Ann Arbor, Michigan, on October 28, 1977. The compound was a white powder and was identified as "Tetrabromobisphenol A, Lot 1021-85" (BP-4A according to packing slip).

III. CLINICAL STUDIES

A. METHOD:

1. General Procedure:

Sixteen male (weighing from 1886 to 2284 grams) and 16 female (weighing from 2030 to 2311 grams) New Zealand White rabbits obtained from Sweetwater Farms, Hillsboro, Ohio, were used in this study. The rabbits were distributed among the groups using a computer-generated table of random numbers. The rabbits were housed individually in hanging wire mesh cages and maintained in a temperature-, humidity- and light-controlled room. Water and Purina® Rabbit Chow® were available ad libitum.

Because the rabbit supplier could not provide healthy rabbits in accordance with the orginal schedule, the shipment was rescheduled. For this reason the conditioning period was limited to five days rather than two weeks originally called for in the protocol.

The study was initiated on December 19, 1977. Terminal sacrifices were conducted on January 9, 1978.

2. Compound Administration:

BP-4A was applied at dosage levels of 100, 500 and 2500 mg/kg/day, five days a week, for a total of 15 applications. Four male and four female rabbits were used at each dosage level and also in a control group. The control rabbits were administered 1.5 ml/kg of 0.9% physiological saline on the same regimen as the treated rabbits. For each dosage level the compound was mixed with saline solution to form a paste.

The back (approximately 10% of the body area) of each rabbit was clipped with an electric clipper as necessary during the study. The skin of one-half the rabbits in each group was abraded twice each week by producing shallow incisions with a scalpel blade. Gentle inunction with a glass stirring rod was used to evenly distribute the

material over the prescribed area. Following the compound application the rabbits were restrained by the use of a collar and returned to their cages. Excess test material was wiped off with a cloth at the end of approximately six hours of exposure and the collars were removed. Individual daily doses were based upon the body weights obtained weekly.

3. Observations:

The rabbits were observed daily for signs of overt toxicity, moribundity and mortality. Signs of dermal irritation were scored and recorded for each rabbit daily following the six hour application period. Prior to the next day application the dermal irritation again was observed and recorded. Individual body weights were obtained weekly.

4. Laboratory Tests:

Once in the pretest period and at 3 weeks of study, blood and urine samples were obtained from all rabbits for analysis. The rabbits were fasted overnight prior to the collection of the samples. Blood samples were obtained from the ear vein of the animals.

a. Hematology:

Hematological studies included hemoglobin[1], hematocrit[2], erythrocyte count[3] and leucocyte count (total[3] and differential).

b. Biochemistry:

Biochemical studies included blood urea nitrogen (BUN)[4], fasting glucose[4], serum alkaline phosphatase[4], serum glutamic oxalacetic transaminase (SGOT)[5], serum glutamic pyruvic transaminase (SGPT)[4], calcium[6], inorganic phosphorus[7] total protein[7] and albumin[4].

c. Urinalysis:

Urinalysis included the determination of volume specific gravity, color and appearance, pH[8], and qualitative tests for albumin[8], glucose[8], ketones[8], occult blood[8] and bilirubin[8].

5. Statistical Analysis:

All statistical analysis compared the treatment groups with the control group, by sex.

Body weights, hematological, biochemical and urinalysis parameters (terminal) and absolute and relative organ weights were compared by analysis of variance (one-way classification), Bartlett's test for homogeneity of variances and the appropriate t-test (for equal or unequal variances) as described by Steel and Torrie[9] using Dunnett's[10] multiple comparison tables to judge significance of differences.

B. RESULTS:

1. General Behavior, Appearance and Survival:

There was no mortality in any group. The animals did not show any signs of systemic toxicity or unusual behavior.

At the 100-mg/kg/day dosage level the compound elicited very slight erythema in study day 3 for one abraded and one intact rabbit. The very slight erythema intermittently appeared for a total of five observations for the abraded and four observations for the intact rabbits.

The 500-mg/kg/day dosage level elicited very slight erythema for all the rabbits, usually appearing on the second day of the study and persisting for 1 to 3 days. For one rabbit for only 1 day the erythema was accompanied by very slight atonia.

At the 2500-mg/kg/day dosage level very slight erythema was noted for all but two rabbits. For most of the rabbits the erythema initially was noted at study day 1 and was intermittent before persisting for several days for two rabbits. For one rabbit the very slight erythema initially appeared in study day 3 and persisted for 10 days. No other signs of dermal irritation were observed for this group of rabbits.

2. Body Weights (Table 1):

Changes in the body weights were similar for the control and treated rabbits.

3. Laboratory Tests (Tables 2-10):

a. Hematology:

No noteworthy pathological changes were seen in the hematological studies.

b. Biochemistry:

No pathological changes were seen in the biochemistry determinations.

c. Urinalysis:

No changes considered to be related to compound were seen in the urinalysis.

IV. PATHOLOGICAL STUDIES

A. METHODS:

1. Gross Pathology:

After completion of the compound administration period all rabbits were sacrificed with an overdose of sodium pentobarbital and necropsied. At necropsy the spleen, liver, adrenals, testes/ovaries, thyroid/parathyroid, brain and kidneys were weighed and representative tissues and organs were collected in buffered neutral 10% formalin.

Fixed tissues from the control and 2500-mg/kg/day rabbits were hand delivered to Mr. Richard Verfuerth, American HistoLabs, Inc. for histological processing. Upon completion of processing, the slides were returned to International Research and Development Corporation for microscopic examination.

2. Histopathology:

Microscopic examination of formalin fixed hematoxylin and eosin stained paraffin sections was performed for all rabbits in the control and 2500-mg/kg/day dosage levels. The following tissues were examined:

skin (treated and untreated)
regional lymph nodes
spleen
pancreas
stomach
duodenum
ileum
jejunum
cecum
colon
mesenteric lymph nodes
liver
gallbladder
adrenals
spinal cord
urinary bladder
prostate/uterus
testes/ovaries
nerve
muscle
bone marrow
thymus
heart
trachea
lung
thyroid,parathyroid
eye
brain (cerebrum, cerebellum and pons)
pituitary
kidneys

any other tissue with lesions.

B. RESULTS:

1. Gross Pathology (Table 11) and Organ Weights (Table 12):

No compound induced gross lesions were observed in any of the rabbits at the terminal sacrifice.

There was a statistically significant increase in mean absolute brain weight for males in the 500-mg/kg/day group. The biological significance of this variation is not known.

2. Histopathology (Table 13):

There were no compound-related microscopic alterations observed in any of the tissues examined. The very slight dermatitis observed in the BP-4A treated skin from one rabbit was not considered significant since similar lesions were observed in the control treated skin from four rabbits. The dermatitis may have been a result of clipper blade irritation or since untreated skin in both groups was similarily affected, the lesion may have been spontaneous in origin.

References

1. Coulter Hemoglobinometer, Coulter Electronics, 590 W. 20th Street, Hialeah, Florida.
2. Microhematocrit, John B. Miale, 3rd Ed., 1967, The C. V. Mosby Company, p. 1154.
3. Coulter Particle Size Counter, Model Z_B, Coulter Electronics, 590 W. 20th Street, Hialeah, Florida.
4. Technicon Auto Analyzer 6/60 Micro Methodology.
5. Sigma Technical Bulletin 505, Sigma Chem. Co., St. Louis, Mo.
6. Atomic Absorption IL Model 353.
7. Micro Auto Analyzer II, 6/60 Micro Methodology.
8. Bililabstix (Ames Reagent Strips).
9. Steel, R. G. D. and Torrie, J. H. (1960), Principles and Procedures of Statistics, McGraw-Hill, New York, N. Y.
10. Dunnett, C. W., New Tables for Multiple Comparisons With a Control, Biometrics, Sept. 1964.

BP-4A: Three Week Dermal Toxicity Study in Rabbits.

TABLE 1. Individual Weekly Body Weights, Grams.

Group, Rabbit Number	Sex	Skin Prep.**	Control		Week of Study		
			-1	0	1	2	3
Control:							
31609	M	A	1836	2012	2190	2432	2496
31611	M	A	1984	2097	2277	2143	1958
31615	M	I	2104	2146	2433	2535	2522
31651	M	I	2146	2210	2524	2705	2387
Mean			2018	2116	2356	2454	2341
31616	F	I	2151	2260	2643	2903	2877
31626	F	I	2130	2150	2386	2612	2503
31640	F	A	2098	2170	2482	2688	2790
31652	F	A	2106	2202	2423	2708	2811
Mean			2121	2196	2484	2728	2745
100 mg/kg/day:							
31623	M	I	1998	2201	2468	2743	2732
31625	M	A	2162	2253	2492	2662	2576
31637	M	I	2209	2284	2484	2713	2619
31639	M	A	2134	2233	2451	2582	2513
Mean			2126	2243	2474	2675	2610
31606	F	A	1994	2069	2385	2582	2555
31628	F	I	1994	2105	2319	2507	2148
31630	F	A	1942	2030	2161	2497	2517
31644	F	I	2086	2122	2318	2627	2572
Mean			2004	2082	2296	2553	2448*

*Significantly different from control mean, $p<0.01$

** I - Intact
A - Abraded

TABLE 1. Cont. Individual Weekly Body Weights, Grams.

Group, Rabbit Number	Sex	Skin Prep.**	Control		Week of Study		
			-1	0	1	2	3
500 mg/kg/day:							
31613	M	A	2195	2256	2352	2568	2518
31619	M	A	1963	2115	2468	2583	2550
31621	M	I	1787	1988	2250	2414	2452
31635	M	I	2182	2200	2432	2349	2325
Mean			2032	2140	2376	2479	2461
31608	F	A	1950	2135	2328	2546	2620
31620	F	I	2142	2213	2541	2663	2536
31624	F	A	2022	2056	2332	2465	2390
31648	F	I	2080	2130	2346	2498	2394
Mean			2049	2134	2387	2543	2485
2500 mg/kg/day:							
31629	M	I	1860	1886	2025	2118	2105
31631	M	A	2135	2147	2371	2407	2215
31633	M	I	2306	2375	2388	2548	2633
31649	M	A	2210	2220	2074	2427	2428
Mean			2128	2157	2215	2375	2345
31612	F	I	2028	2184	2386	2557	2506
31618	F	A	2217	2311	2661	2888	2779
31632	F	A	2027	2075	2446	2567	2562
31642	F	I	2068	2231	2461	2727	2711
Mean			2085	2200	2489	2685	2640

** I - Intact
A - Abraded

BP-4A: Three Week Dermal Toxicity Study in Rabbits.

TABLE 2. MALES: Means and Significance[a] of Hematological Values.

Hematology	Week of Study	Control	100 mg/kg/day	500 mg/kg/day	2500 mg/kg/day
Erythrocytes, 10^6/cmm	Pretest	5.27	5.08	5.18	4.99
	3	5.29		5.47	5.08
Hemoglobin, g/100 ml	Pretest	13.1	12.4	13.0	12.4
	3	11.8	12.3	12.4	11.6
Hematocrit, %	Pretest	41	39	39	39
	3	40	41	41	37
Leucocytes, 10^3/cmm	Pretest	9.11	7.48	7.32	6.86
	3	7.89	9.79	7.87	7.06
Neutrophils, %	Pretest	47	31	37	35
	3	51	39	28	34
Lymphocytes, %	Pretest	50	67	62	63
	3	47	58	69	64
Eosinophils, %	Pretest	1	2	0	0
	3	1	0	1	0
Monocytes, %	Pretest	0	0	0	0
	3	1	3	2	2
Basophils, %	Pretest	2	0	1	2
	3	0	0	0	0

[a]Statistical analysis conducted on 3-week values only

TABLE 2. Cont. FEMALES: Means and Significance[a] of Hematological Values.

Hematology	Week of Study	Control	100 mg/kg/day	500 mg/kg/day	2500 mg/kg/day
Erythrocytes, 10^6/cmm	Control	4.87	4.97	4.92	4.91
	3	5.17	5.23	5.40	5.43
Hemoglobin, g/100 ml	Control	12.2	12.4	11.9	12.2
	3	11.6	11.6	12.6	12.3
Hematocrit, %	Control	38	38	38	37
	3	40	38	41	40
Leucocytes, 10^3/cmm	Control	6.57	7.23	6.38	6.55
	3	6.94	5.93	7.96	5.09
Neutrophils, %	Control	35	43	37	27
	3	33	30	22	35
Lymphocytes, %	Control	62	56	61	70
	3	65	67	77	63
Eosinophils, %	Control	1	1	1	1
	3	0	1	0	0
Monocytes, %	Control	0	0	0	0
	3	2	2	1	2
Basophils, %	Control	2	0	1	2
	3	0	0	0	0

[a]Statistical analysis conducted on 3-week values only

BP-4A: Three Week Dermal Toxicity Study in Rabbits.

TABLE 3. Individual Hematological Values - Pretest.

Group, Rabbit Number	Sex	Erythrocytes 10^6/cmm	Erythrocyte Appear.	Hemoglobin g/100 ml	Hematocrit %	Leucocytes 10^3/cmm	Neutrophils Seg. %	Neutrophils Non-Seg. %	Lymphocytes %	Eosinophils %	Monocytes %	Basophils %
Control:												
31609	M	5.32	N	12.9	42	9.21	41	0	59	0	0	0
31611	M	5.36	N	13.2	41	7.79	62	0	38	0	0	0
31615	M	5.29	N	13.2	40	10.42	40	0	55	1	0	4
31651	M	5.10	N	13.1	40	9.02	43	0	52	2	0	3
Mean		5.27		13.1	41	9.11	47	0	50	1	0	2
31616	F	4.81	N	11.4	37	4.61	41	0	57	0	0	2
31626	F	4.96	N	12.4	39	7.37	36	0	63	0	0	1
31640	F	5.05	N	13.0	38	5.93	27	0	67	3	0	3
31652	F	4.65	N	12.1	36	8.35	37	0	61	2	0	0
Mean		4.87		12.2	38	6.57	35	0	62	1	0	2
100 mg/kg/day:												
31623	M	4.76	1+P	11.1	35	7.86	45	0	47	7	0	1
31625	M	5.36	N	13.2	40	7.72	19*	0	79*	2*	0	0
31637	M	5.04	1+P	12.5	39	7.41	39	0	61	0	0	0
31639	M	5.16	N	12.7	41	6.93	20	0	80	0	0	0
Mean		5.08		12.4	39	7.48	31	0	67	2	0	0
31606	F	4.99	N	13.0	39	8.57	56	0	44	0	0	0
31628	F	4.89	N	12.0	38	7.42	55	0	44	1	0	0
31630	F	5.02	N	12.5	38	7.31	37	0	63	0	0	0
31644	F	4.96	N	12.1	37	5.63	23	0	73	3	0	1
Mean		4.97		12.4	38	7.23	43	0	56	1	0	0
500 mg/kg/day:												
31613	M	5.41	N	13.7	42	5.69	48	0	52	0	0	0
31619	M	5.40	1+P	13.3	38	7.64	38	0	60	1	0	1
31621	M	5.21	N	13.5	41	7.68	31	0	68	0	0	1
31635	M	4.70	N	11.6	36	8.25	32	0	68	0	0	0
Mean		5.18		13.0	39	7.32	37	0	62	0	0	1
31608	F	5.31	N	12.7	40	9.74	32	1	63	1	1	2
31620	F	4.84	N	11.6	37	5.27	28	0	70	2	0	0
31624	F	4.98	N	12.5	40	5.17	62	0	38	0	0	0
31648	F	4.53	N	10.9	36	5.32	24	0	76	0	0	0
Mean		4.92		11.9	38	6.38	37	0	61	1	0	1
2500 mg/kg/day:												
31629	M	4.97	N	12.6	40	6.99	29	0	71	0	0	0
31631	M	5.37	N	13.7	42	4.62	30	0	67	0	0	3
31633	M	5.01	1+P	11.9	37	4.06	50	0	50	0	0	0
31649	M	4.59	N	11.5	37	11.77	29	0	67	0	0	4
Mean		4.99		12.4	39	6.86	35	0	63	0	0	2
31612	F	4.74	N	12.2	37	5.52	22	0	73	2	0	3
31618	F	4.86	1+P	11.5	35	4.16	35	0	64	0	0	1
31632	F	5.01	N	11.9	37	9.31	19	0	77	2	0	2
31642	F	5.04	N	13.0	38	7.00	34	0	66	0	0	0
Mean		4.91		12.2	37	6.55	27	0	70	1	0	2

N - Normal
P - Polychromasia
* Repeat determination

3P-4A: Three Week Dermal Toxicity Study in Rabbits.

TABLE 4. Individual Hematological Values - 3 Weeks.

Group, Rabbit Number	Sex	Erythrocytes 10^6/cmm	Erythrocyte Appear.	Hemoglobin g/100 ml	Hematocrit %	Leucocytes 10^3/cmm	Neutrophils Seg. %	Neutrophils Non-Seg. %	Lymphocytes %	Eosinophils %	Monocytes %	Basophils %
Control:												
31609	M	5.08	1+P	11.5	39	6.45	32	0	66	1	1	0
31611	M	4.91	N	11.3	37	7.29	48	0	50	1	1	0
31615	M	5.32	N	12.6	41	6.64	62	0	38	0	0	0
31651	M	5.85	N	11.7	41	11.16	60	0	37	0	3	0
Mean		5.29		11.8	40	7.89	51	0	47	1	1	0
31616	F	5.23	N	11.7	40	5.69	32	0	66	1	1	0
31626	F	5.68	N	13.1	44	7.70	29	0	67	0	4	0
31640	F	5.18	N	11.3	38	6.07	22	0	76	0	2	0
31652	F	4.59	2+P	10.4	36	8.30	49	0	50	0	1	0
Mean		5.17		11.6	40	6.94	33	0	65	0	2	0
100 mg/kg/day:												
31623	M	5.15	N	11.2	37	6.70	49	0	46	0	5	0
31625	M	5.42	N	13.0	42	13.54	40	0	59	0	1	0
31637	M	5.27	1+P	11.7	40	7.63	54	1	43	0	2	0
31639	M	5.48	1+P	13.4	43	11.30	11	0	85	1	3	0
Mean		5.33		12.3	41	9.79	39	0	58	0	3	0
31606	F	5.15	N	12.1	35	5.95	39	0	59	0	2	0
31628	F	5.04	N	10.5	37	6.32	27	0	72	0	1	0
31630	F	5.27	N	11.6	39	7.03	34	0	63	1	2	0
31644	F	5.46	N	12.1	41	4.41	21	0	75	1	3	0
Mean		5.23		11.6	38	5.93	30	0	67	1	2	0
500 mg/kg/day:												
31613	M	5.27	N	12.2	42	7.11	33	0	63	1	3	0
31619	M	5.40	N	11.6	38	4.88	23	0	76	0	1	0
31621	M	5.60	1+P	13.0	41	8.46	20	0	78	0	2	0
31635	M	5.61	N	12.6	42	11.03	34	0	64	1	1	0
Mean		5.47		12.4	41	7.87	28	0	69	1	2	0
31608	F	5.80	N	12.8	41	8.95	9	0	91	0	0	0
31620	F	5.46	N	12.8	40	10.83	32	0	67	1	0	0
31624	F	5.58	N	13.3	43	5.42	29	0	71	0	0	0
31648	F	4.77	N	11.6	38	6.64	18	0	78	0	4	0
Mean		5.40		12.6	41	7.96	22	0	77	0	1	0
2500 mg/kg/day:												
31629	M	5.19	1+P	11.8	37	6.65	31	0	68	0	1	0
31631	M	4.45	1+P	10.3	35	9.43	48	0	51	0	2	0
31633	M	5.68	N	12.5	38	4.09	30	0	67	0	3	0
31649	M	4.98	N	11.6	39	8.06	28	0	70	1	1	0
Mean		5.08		11.6	37	7.06	34	0	64	0	2	0
31612	F	5.31	N	12.2	39	4.31	24	0	74	1	1	0
31618	F	5.16	1+P	11.3	38	4.18	48	0	50	0	2	0
31632	F	5.47	1+P	12.5	41	6.62	47	0	51	0	2	0
31642	F	5.76	N	13.0	41	5.24	19	0	79	0	2	0
Mean		5.43		12.3	40	5.09	35	0	63	0	2	0

N - Normal
P - Polychromasia

BP-4A: Three Week Dermal Toxicity Study in Rabbits.

TABLE 5. MALES: Means and Significance[a] of Biochemical Values.

Biochemistry	Week of Study	Control	100 mg/kg/day	500 mg/kg/day	2500 mg/kg/day
Glucose, mg/100 ml	Pretest	131	125	132	124
	3	126	128	134	128
B.U.N., mg/100 ml	Pretest	18.4	18.5	21.2	18.4
	3	19.7	20.1	19.7	20.7
Alkaline Phosphatase, int'l u/l	Pretest	192	207	168	215
	3	151	232	200	220
S.G.O.T., Sigma units/ml	Pretest	20	28	19	26
	3	19	32	27	30*
S.G.P.T., int'l u/l	Pretest	63	87	72	91
	3	55	75	80	83
Calcium, mg/100 ml	Pretest	12.8	12.5	12.8	12.9
	3	12.2	13.1	12.8	12.4
Inorganic Phosphorus, mg/100 ml	Pretest	6.9	7.9	7.4	7.9
	3	7.6	8.3	8.3	7.3
Total Protein, g/100 ml	Pretest	6.01	5.84	5.94	6.32
	3	6.05	6.69	6.38	5.96
Albumin, g/100 ml	Pretest	3.84	3.74	3.89	3.98
	3	4.07	4.73	4.48	3.99

[a]Statistical analysis conducted on 3-week values only
*Significantly different from the control mean, $p>0.05$

BP-4A: Three Week Dermal Toxicity Study in Rabbits.

TABLE 5. Cont. FEMALES: Means and Significance[a] of Biochemical Values.

Biochemistry	Week of Study	Control	100 mg/kg/day	500 mg/kg/day	2500 mg/kg/day
Glucose, mg/100 ml	Control	131	143	135	135
	3	126	135	134	142**
B.U.N., mg/100 ml	Control	20.3	22.9	16.7	18.5
	3	26.2	22.8	23.3	27.1
Alkaline Phosphatase, int'l u/l	Control	226	216	194	206
	3	217	210	199	249
S.G.O.T., Sigma units/ml	Control	22	17	16	32
	3	19	19	19	25
S.G.P.T., int'l u/l	Control	65	66	71	75
	3	58	76	81	76
Calcium, mg/100 ml	Control	12.7	12.1	12.8	12.2
	3	13.1	13.3	12.7	12.2
Inorganic Phosphorus, mg/100 ml	Control	7.6	7.6	7.0	7.7
	3	8.1	7.3	7.9	8.1
Total Protein, g/100 ml	Control	5.92	5.94	5.82	5.97
	3	6.42	6.41	6.60	6.73
Albumin, g/100 ml	Control	3.76	4.11	3.88	3.87
	3	4.79	4.74	4.72	4.83

[a]Statistical significance conducted on 3-week values only
**Significantly different from the control mean, $p<0.01$

Three Week Dermal Toxicity Study in Rabbits.

TABLE 6.

Individual Biochemical Values - Pretest.

Group, Rabbit Number	Sex	Glucose mg/100 ml	B.U.N. mg/100 ml	Total Protein g/100 ml	Albumin g/100 ml	Alk. Phos. Int'l units/ml	S.G.O.T. Sigma units/ml	S.G.P.T. Int'l units/l	Inorganic Phosphorus mg/100 ml	Calcium mg/100 ml
Control:										
31609	M	126	18.2	6.36	3.98	132	17	51	6.4	12.4
31611	M	148	11.5	6.28	3.94	266	36	73	6.2	12.8
31615	M	119	20.1	5.68	3.61	131	11	80	7.0	13.0
31651	M	131	23.9	5.70	3.81	239	17	46	7.8	12.8
Mean		131	18.4	6.01	3.84	192	20	63	6.9	12.8
31616	F	130	21.2	6.18	4.21	174	19	70	6.6	13.4
31626	F	130	20.0	5.90	3.98	227	18	51	8.2	12.6
31640	F	120	25.8	6.12	3.35	248	17	64	8.0	12.2
31652	F	144	14.0	5.48	3.50	256	32	75	7.6	12.6
Mean		131	20.3	5.92	3.76	226	22	65	7.6	12.7
100 mg/kg/day:										
31623	M	126	18.6	5.86	3.83	253	39	86	8.0	12.6
31625	M	130	20.0	5.44	3.52	300	26	84	7.6	13.4
31637	M	111	21.0	5.76	3.51	140	26	89	7.6	11.4
31639	M	133	14.2	6.30	4.10	134	20	88	8.4	12.4
Mean		125	18.5	5.84	3.74	207	28	87	7.9	12.5
31606	F	126	23.7	5.62	3.91	228	17	64	8.4	11.8
31628	F	137	24.2	6.12	4.11	165	18	73	7.6	12.4
31630	F	156	26.1	5.82	4.10	208	16	69	6.2	11.8
31644	F	151	17.7	6.18	4.32	264	16	57	8.0	12.4
Mean		143	22.9	5.94	4.11	216	17	66	7.6	12.1

TABLE 6. Cont. Individual Biochemical Values - Pretest.

Group, Rabbit Number	Sex	Glucose mg/100 ml	B.U.N. mg/100 ml	Total Protein g/100 ml	Albumin g/100 ml	Alk. Phos. Int'l units/ml	S.G.O.T. Sigma units/ml	S.G.P.T. Int'l units/l	Inorganic Phosphorus mg/100 ml	Calcium mg/100 ml
500 mg/kg/day:										
31613	M	130	18.1	5.84	4.01	185	20	88	7.0	13.2
31619	M	128	19.1	5.86	3.89	181	14	65	6.8	12.0
31621	M	131	30.9	5.68	3.50	121	22	75	8.4	13.4
31635	M	137	16.8	6.36	4.16	186	19	59	7.4	12.4
Mean		132	21.2	5.94	3.89	168	19	72	7.4	12.8
31608	F	131	15.2	5.72	3.63	214	13	50	7.0	13.4
31620	F	138	18.7	6.08	4.08	190	18	70	7.0	12.8
31624	F	131	17.9	5.86	3.91	143	17	98	6.8	12.4
31648	F	140	14.8	5.60	3.89	230	14	65	7.2	12.6
Mean		135	16.7	5.82	3.88	194	16	71	7.0	12.8
2500 mg/kg/day:										
31629	M	120	19.9	6.24	3.99	159	24	89	7.6	13.4
31631	M	124	17.9	6.60	3.97	231	27	99	8.2	13.0
31633	M	126	22.0	6.32	3.82	241	29	104	7.8	12.6
31649	M	127	13.9	6.12	4.15	230	24	71	7.8	12.6
Mean		124	18.4	6.32	3.98	215	26	91	7.9	12.9
31612	F	131	19.0	5.46	3.79	225	37	60	7.8	12.0
31618	F	146	15.9	5.92	3.99	182	29	102	7.4	12.4
31632	F	130	19.0	6.32	3.70	251	41	79	6.8	11.0
31642	F	132	20.0	6.18	4.00	167	22	59	8.6	13.4
Mean		135	18.5	5.97	3.87	206	32	75	7.7	12.2

TABLE 7. Individual Biochemical Values - 3 Weeks.

Group, Rabbit Number	Sex	Glucose mg/100 ml	B.U.N. mg/100 ml	Total Protein g/100 ml	Albumin g/100 ml	Alk. Phos. Int'l units/ml	S.G.O.T. Sigma units/ml	S.G.P.T. Int'l units/l	Inorganic Phosphorus mg/100 ml	Calcium mg/100 ml
Control:										
31609	M	117	17.3	6.90	4.90	180	22	64	7.7	12.6
31611	M	118	18.4	5.06	2.98	88	17	39	6.8	11.6
31615	M	136	22.9	6.75	4.88	145	18	73	8.3	13.5
31651	M	134	20.0	5.47	3.52	192	17	44	7.5	11.2
Mean		126	19.7	6.05	4.07	151	19	55	7.6	12.2
31616	F	127	27.0	6.60	5.03	221	23	59	7.5	13.3
31626	F	131	26.9	5.92	4.29	159	17	57	8.6	12.8
31640	F	120	27.9	6.42	4.78	237	17	56	8.5	13.1
31652	F	127	22.9	6.73	5.04	251	17	61	7.6	13.2
Mean		126	26.2	6.42	4.79	217	19	58	8.1	13.1
100 mg/kg/day:										
31623	M	125	23.1	6.26	4.54	337	64	63	8.9	12.6
31625	M	133	21.9	7.09	4.88	283	17	96	9.3	13.6
31637	M	116	17.0	6.35	4.39	162	18	62	7.0	12.4
31639	M	136	18.4	7.04	5.11	144	27	79	7.9	13.7
Mean		128	20.1	6.69	4.73	232	32	75	8.3	13.1
31606	F	136	23.9	6.45	4.78	264	19	54	7.8	13.7
31628	F	143	20.5	6.51	4.69	123	13	93	6.0	14.1
31630	F	127	23.0	6.41	4.79	226	23	109	8.1	12.6
31644	F	134	23.9	6.26	4.68	225	20	47	7.4	12.6
Mean		135	22.8	6.41	4.74	210	19	76	7.3	13.3

TABLE 7. Cont. Individual Biochemical Values - 3 Weeks.

Group, Rabbit Number	Sex	Glucose mg/100 ml	B.U.N. mg/100 ml	Total Protein g/100 ml	Albumin g/100 ml	Alk. Phos. Int'l units/ml	S.G.O.T. Sigma units/ml	S.G.P.T. Int'l units/l	Inorganic Phosphorus mg/100 ml	Calcium mg/100 ml
500 mg/kg/day:										
31613	M	127	17.7	6.10	4.41	155	23	69	7.4	13.1
31619	M	151	18.9	6.22	4.71	259	23	64	7.7	12.3
31621	M	130	24.1	6.46	4.80	256	17	84	8.9	13.5
31635	M	127	18.2	6.74	3.99	130	46	99	9.2	12.4
Mean		134	19.7	6.38	4.48	200	27	80	8.3	12.8
31608	F	131	22.1	6.15	4.50	259	16	64	7.5	12.8
31620	F	137	22.1	7.43	5.25	217	25	127	8.3	12.9
31624	F	130	24.0	6.24	4.71	135	17	72	7.3	12.4
31648	F	136	25.0	6.56	4.43	186	17	61	8.6	12.7
Mean		134	23.3	6.60	4.72	199	19	81	7.9	12.7
2500 mg/kg/day:										
31629	M	126	24.3	5.99	4.22	257	24	80	7.5	13.7
31631	M	121	18.0	5.46	3.06	96	26	53	6.6	11.7
31633	M	137	23.0	6.28	4.32	250	34	113	7.5	12.3
31649	M	126	17.5	6.09	4.37	277	35	84	7.5	11.7
Mean		128	20.7	5.96	3.99	220	30	83	7.3	12.4
31612	F	144	30.3	6.44	4.70	313	24	76	8.5	11.5
31618	F	148	26.8	6.84	4.97	164	13	65	7.9	12.9
31632	F	136	27.1	7.13	5.11	291	46	106	7.3	11.9
31642	F	140	24.1	6.50	4.52	227	15	58	8.6	12.5
Mean		142	27.1	6.73	4.83	249	25	76	8.1	12.2

BP-4A: Three Week Dermal Toxicity Study in Rabbits.

TABLE 8. MALES: Means and Significance[a] of Urinalysis Values.

Urinalysis	Week of Study	Control	100 mg/kg/day	500 mg/kg/day	2500 mg/kg/day
Volume, ml	Control	44	61	71	86
	3	176	298	166	209
pH	Control	7.2	8.6	7.4	9.0
	3	8.6	8.5	8.4	8.5
Specific Gravity	Control	1.028	1.017	1.021	1.018
	3	1.025	1.021	1.020	1.026

[a]Statistical significance conducted on 3-week values only

TABLE 8. Cont. FEMALES: Means and Significance[a] of Urinalysis Values.

Urinalysis	Week of Study	Control	100 mg/kg/day	500 mg/kg/day	2500 mg/kg/day
Volume, ml	Control	60	155	86	172
	3	363	331	353	328
pH	Control	8.5	8.6	8.8	8.5
	3	8.6	8.5	8.6	8.5
Specific Gravity	Control	1.022	1.018	1.023	1.016
	3	1.022	1.020	1.022	1.024

[a]Statistical significance conducted on 3-week values only

TABLE 9. Individual Urinalysis Values - Pretest.

Group, Rabbit Number	Sex	Volume ml	Color and Appearance	pH	Specific Gravity	Albumin	Glucose	Bilirubin	Occult Blood	Ketones
Control:										
31609	M	12	Normal	5.4	1.035	N	N	N	N	N
31611	M	0								
31615	M	75	Normal	9.0	1.021	N	N	N	N	N
31651	M	0								
31616	F	75	Normal	7.9	1.014	N	N	N	N	N
31626	F	50	Normal	8.0	1.030	N	N	N	N	N
31640	F	25	Normal	9.0	1.022	N	N	N	N	N
31652	F	90	Normal	9.0	1.020	N	N	N	N	N
100 mg/kg/day:										
31623	M	70	Normal	8.8	1.012	N	N	N	N	N
31625	M	105	Normal	8.0	1.013	N	N	N	N	N
31637	M	30	Normal	9.0	1.024	N	N	N	N	N
31639	M	40	Normal	8.5	1.019	N	N	N	N	N
31606	F	225	Normal	8.0	1.010	N	N	N	N	N
31628	F	225	Normal	8.5	1.006	N	N	N	N	N
31630	F	135	Normal	8.9	1.009	N	N	N	N	N
31644	F	35	Normal	9.0	1.045	N	N	N	N	N
500 mg/kg/day:										
31613	M	60	Normal	8.5	1.035	N	N	N	N	N
31619	M	75	Normal	6.2	1.010	N	N	N	N	N
31621	M	90	Normal	5.9	1.015	N	N	N	N	N
31635	M	60	Normal	9.0	1.022	N	N	N	N	N
31608	F	65	Normal	9.0	1.030	N	N	N	N	N
31620	F	115	Normal	8.0	1.020	N	N	N	N	N
31624	F	110	Normal	9.0	1.020	N	N	N	N	N
31648	F	55	Normal	9.0	1.021	N	N	N	N	N
2500 mg/kg/day:										
31629	M	100	Normal	8.9	1.015	N	N	N	N	N
31631	M	125	Normal	9.0	1.015	N	N	N	N	N
31633	M	25	Normal	9.0	1.023	N	N	N	N	N
31649	M	95	Normal	8.9	1.020	N	N	N	1+	N
31612	F	250	Normal	7.4	1.012	N	N	N	N	N
31618	F	185	Normal	9.0	1.011	N	N	N	N	N
31632	F	0								
31642	F	80	Normal	9.0	1.025	N	N	N	N	N

Code: tr - Trace
1+ - Trace to slight
2+ - Slight to moderate
3+ - Moderate
4+ - Marked
N - Negative

3P-4A: Three Week Dermal Toxicity Study in Rabbits.

TABLE 10. Individual Urinalysis Values - 3 Weeks.

Group, Rabbit Number	Sex	Volume ml	Color and Appearance	pH	Specific Gravity	Albumin	Glucose	Bilirubin	Occult Blood	Ketones
Control:										
31609	M	190	Normal	8.5	1.027	N	N	N	2+	N
31611	M	90	Normal	8.5	1.027	N	N	N	2+	N
31615	M	195	Normal	9.0	1.027	N	N	N	2+	N
31651	M	230	Normal	8.5	1.017	N	N	N	3+	N
31616	F	480	Normal	8.5	1.015	N	N	N	3+	N
31626	F	350	Normal	9.0	1.022	N	N	N	2+	N
31640	F	295	Normal	8.5	1.025	N	N	N	2+	N
31652	F	325	Normal	8.5	1.025	N	N	N	2+	N
100 mg/kg/day:										
31623	M	280	Normal	8.5	1.022	N	N	N	2+	N
31625	M	200	Normal	8.5	1.017	N	N	N	1+	N
31637	M	310	Normal	8.5	1.025	N	N	N	1+	N
31639	M	400	Normal	8.5	1.018	N	N	N	1+	N
31606	F	475	Normal	8.5	1.020	N	N	N	2+	N
31628	F	375	Normal	8.5	1.017	N	N	N	2+	N
31630	F	200	Normal	8.5	1.026	N	N	N	2+	N
31644	F	275	Normal	8.5	1.018	N	N	N	2+	N
500 mg/kg/day:										
31613	M	280	Normal	8.5	1.022	N	N	N	2+	N
31619	M	50	Normal	8.5	1.022	N	N	N	2+	N
31621	M	80	Normal	8.5	1.022	N	N	N	2+	N
31635	M	255	Normal	8.0	1.015	N	N	N	1+	N
31608	F	205	Normal	8.5	1.016	N	N	N	2+	N
31620	F	375	Normal	8.5	1.025	N	N	N	2+	N
31624	F	440	Normal	8.5	1.022	N	N	N	1+	N
31648	F	390	Normal	9.0	1.025	N	N	N	1+	N
2500 mg/kg/day:										
31629	M	235	Normal	8.5	1.023	N	N	N	tr	N
31631	M	175	Normal	8.5	1.027	N	N	N	tr	N
31633	M	115	Normal	8.5	1.025	N	N	N	tr	N
31649	M	310	Normal	8.5	1.027	N	N	N	tr	N
31612	F	205	Normal	8.5	1.027	N	N	N	1+	N
31618	F	470	Normal	8.5	1.025	N	N	N	2+	N
31632	F	325	Normal	8.5	1.020	N	N	N	1+	N
31642	F	310	Normal	8.5	1.025	N	N	N	1+	N

Code: tr - Trace
1+ - Trace to slight
2+ - Slight to moderate
3+ - Moderate
4+ - Marked
N - Negative

Three Week Dermal Toxicity Study in Rabbits.

TABLE II. Necropsy Observations.

Site / Lesion	Group, Rabbit Number	Control								100 mg/kg/day								500 mg/kg/day								2500 mg/kg/day							
	Sex	M	M	M	M	F	F	F	F	M	M	M	M	F	F	F	F	M	M	M	M	F	F	F	F	M	M	M	M	F	F	F	F
		31609	31611	31615	31651	31616	31626	31640	31652	31623	31625	31637	31639	31606	31638	31630	31644	31613	31619	31621	31635	31608	31620	31624	31643	31629	31631	31633	31649	31612	31618	31632	31642
No gross lesions					x	x	x	x				x	x	x		x	x		x		x	x	x	x		x		x	x		x		x
External																																	
subcutaneous hemorrhage, cervical region									x																								
Lungs																																	
congestion		x	x																	x				x			x			x			
reddish-tan mottled discoloration				x																													
firm tan focus											x																						
adhesions, abscess																																x	
Liver																																	
yellow foci										x	x																						
gray-white foci															x																		
yellow nodule																									x								
Abdominal Cavity																																	
firm, lobulated mass																		x															
Kidneys																																	
thickened capsule, unilateral																		x															
Uterus																																	
enlarged																																x	
Ovaries																																	
pale yellow foci, unilateral																																x	

TABLE 12. Absolute (Grams) and Relative (% Body Weight) Organ Weights.

Group, Rabbit Number	Sex	Body Wt. g	Spleen g	Spleen %x10[2]	Liver g	Liver %	Adrenals g	Adrenals %x10[2]	Testes/ Ovaries g	Testes/ Ovaries %x10[2]	Thyroid Parathyroid g	Thyroid Parathyroid %x10[2]	Brain g	Brain %	Kidneys g	Kidneys %
Control:																
31609	M	2496	0.78	3.13	102.09	4.09	0.26	1.04	2.32	0.09	0.23	0.92	8.98	0.36	22.07	0.88
31611	M	1958	1.05	5.36	66.93	3.42	0.20	1.02	3.96	0.20	0.29	1.48	8.28	0.42	14.43	0.74
31615	M	2522	1.50	5.95	110.29	4.37	0.34	1.35	3.31	0.13	0.44	1.74	8.63	0.34	15.50	0.61
31651	M	2387	1.08	4.52	67.69	2.84	0.26	1.09	2.52	0.11	0.21	0.88	8.45	0.35	17.50	0.73
Mean		2341	1.10	4.74	86.75	3.68	0.27	1.13	3.03	0.13	0.29	1.26	8.59	0.37	17.38	0.74
31616	F	2877	1.34	4.66	103.56	3.60	0.30	1.04	0.36	1.25	0.26	0.90	8.43	0.29	19.09	0.66
31626	F	2503	0.92	3.68	87.90	3.51	0.16	0.64	0.22	0.88	0.21	0.84	9.31	0.37	17.95	0.72
31640	F	2790	1.00	3.58	114.46	4.10	0.25	0.90	0.21	0.75	0.23	0.82	8.78	0.31	18.05	0.65
31652	F	2811	1.09	3.88	129.60	4.61	0.39	1.39	0.18	0.64	0.31	1.10	8.26	0.29	21.60	0.77
Mean		2745	1.09	3.95	108.88	3.96	0.28	0.99	0.24	0.88	0.25	0.92	8.70	0.32	19.17	0.70
100 mg/kg/day:																
31623	M	2732	0.79	2.89	95.84	3.51	0.33	1.21	3.78	0.14	0.31	1.13	8.69	0.32	21.15	0.77
31625	M	2576	0.98	3.80	85.72	3.33	0.37	1.44	2.92	0.11	0.24	0.93	9.43	0.37	19.05	0.74
31637	M	2619	2.31	8.82	106.64	4.07	0.26	0.99	2.50	0.10	0.26	0.99	8.61	0.33	18.85	0.72
31639	M	2513	0.98	3.90	92.56	3.68	0.31	1.23	3.21	0.13	0.26	1.03	8.70	0.35	21.66	0.86
Mean		2610	1.27	4.85	95.19	3.65	0.32	1.22	3.10	0.12	0.27	1.02	8.86	0.34	20.18	0.77
31606	F	2555	1.21	4.74	103.77	4.06	0.27	1.06	0.17	0.67	0.28	1.10	7.82	0.31	16.74	0.66
31628	F	2148	1.31	6.10	77.37	3.60	0.30	1.40	0.22	1.02	0.23	1.07	8.26	0.38	16.69	0.78
31630	F	2517	0.69	2.74	90.23	3.58	0.22	0.87	0.19	0.75	0.24	0.95	8.14	0.32	20.77	0.83
31644	F	2572	1.37	5.33	91.66	3.56	0.26	1.01	0.41	1.59	0.26	1.01	8.97	0.35	16.74	0.65
Mean		2448	1.15	4.73	90.76	3.70	0.26	1.08	0.25	1.01	0.25	1.03	8.30	0.34	17.74	0.73
500 mg/kg/day:																
31613	M	2518	1.37	5.44	98.76	3.92	0.52	2.07	2.99	0.12	0.30	1.19	9.00	0.36	17.34	0.69
31619	M	2550	0.93	3.65	107.19	4.20	0.42	1.65	4.19	0.16	0.36	1.41	9.58	0.38	22.23	0.87
31621	M	2452	0.99	4.04	90.93	3.71	0.33	1.35	3.77	0.15	0.31	1.26	9.41	0.38	19.36	0.79
31635	M	2325	1.05	4.52	82.54	3.55	0.25	1.08	3.63	0.16	0.26	1.12	8.85	0.38	16.35	0.70
Mean		2461	1.09	4.41	94.86	3.85	0.38	1.53	3.65	0.15	0.31	1.25	9.21*	0.37	18.82	0.76
31608	F	2620	0.76	2.90	81.15	3.10	0.26	0.99	0.16	0.61	0.28	1.07	8.98	0.34	14.15	0.54
31620	F	2536	1.23	4.85	87.03	3.43	0.20	0.79	0.31	1.22	0.36	1.42	9.46	0.37	17.63	0.70
31624	F	2390	1.07	4.48	100.97	4.22	0.34	1.42	0.17	0.71	0.19	0.79	8.11	0.34	17.87	0.75
31648	F	2394	0.64	2.67	87.40	3.65	0.26	1.09	0.23	0.96	0.27	1.13	9.62	0.40	15.12	0.63
Mean		2485	0.93	3.73	89.14	3.60	0.27	1.07	0.22	0.88	0.28	1.10	9.04	0.36	16.19	0.65

Group mean relative organ weights shown in this table were calculated by averaging the individually calculated relative organ weights.
*Significantly different from control group mean, $p<0.05$.

TABLE 12. Cont. Absolute (Grams) and Relative (% Body Weight) Organ Weights.

Group, Rabbit Number	Sex	Body Wt. g	Spleen g	Spleen %x10[2]	Liver g	Liver %	Adrenals g	Adrenals %x10[2]	Testes/ Ovaries g	Testes/ Ovaries %x10[2]	Thyroid Parathyroid g	Thyroid Parathyroid %x10[2]	Brain g	Brain %	Kidneys g	Kidneys %
2500 mg/kg/day:																
31629	M	2105	0.71	3.37	74.18	3.52	0.34	1.62	2.64	0.13	0.24	1.14	9.05	0.43	15.14	0.72
31631	M	2215	0.90	4.06	72.05	3.25	0.40	1.81	3.23	0.15	0.27	1.22	9.46	0.43	14.20	0.64
31633	M	2633	2.50	9.49	95.11	3.61	0.38	1.44	3.98	0.15	0.43	1.63	9.16	0.35	18.95	0.72
31649	M	2428	0.43	1.77	81.00	3.34	0.32	1.32	2.93	0.12	0.22	0.91	8.91	0.37	19.10	0.79
Mean		2345	1.14	4.68	80.59	3.43	0.36	1.55	3.20	0.14	0.29	1.22	9.15	0.39	16.85	0.72
31612	F	2506	0.62	2.47	94.48	3.77	0.19	0.76	0.15	0.60	0.24	0.96	8.76	0.35	14.79	0.59
31618	F	2779	1.22	4.39	129.85	4.67	0.27	0.97	0.26	0.94	0.23	0.83	9.09	0.33	18.77	0.68
31632	F	2562	1.57	6.13	91.71	3.58	0.40	1.56	0.39	1.52	0.29	1.13	7.61	0.30	16.44	0.64
31642	F	2711	1.12	4.13	87.65	3.23	0.33	1.22	0.28	1.03	0.25	0.92	8.92	0.33	17.35	0.64
Mean		2640	1.13	4.28	100.92	3.81	0.30	1.13	0.27	1.02	0.25	0.96	8.60	0.33	16.84	0.64

Group mean relative organ weights shown in this table were calculated by averaging the individually calculated relative organ weights.

BP-4A: Three Week Dermal Toxicity Study in Rabbits.

TABLE 13. Histomorphologic Observations.

Tissue Lesion	Group, Rabbit Number	Control								2500 mg/kg/day							
	Sex	M	M	M	M	F	F	F	F	M	M	M	M	F	F	F	F
	31609	31611	31615	31651	31616	31626	31640	31652	31629	31631	31633	31649	31612	31618	31632	31642
Skin (Treated)		1	1	1	1					1	1	1	1		1	1	1
focal/multifocal dermal inflammatory infiltrate						2	2	2	2					2			
Skin (Untreated)		1		1	1	1					1	1				1	1
focal/multifocal dermal inflammatory infiltrate			2				2	3	2	2			2	2	2		
focal acanthosis								2									
focal hyperkeratosis								2									
Regional Lymph Nodes		1	-	1	1	1	1	1	1	1	1		1	1	1	1	-
edema												2					
Brain		1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Spinal Cord		1	-	1	1	1	1		1	1	1	1	1	1	1		1
focal hemorrhage								2								2	
Peripheral Nerve (Sciatic)		1	-	-	1	1	1	1	1		1	1	-	1	1	1	1
axonal degeneration										4							
Eye		1	1					1		1			1	1	1	1	1
focal mononuclear infiltrate - corneal-scleral junction				3		3			3			2					
focal inflammatory infiltrate - corneal-scleral junction					2												
retinal cyst							x										
focal mononuclear infiltrate - choroid											2						
Pituitary		1	1	1	1	1	1	1	1	1		1	1	1	1	1	1
focal mononuclear infiltrate											2						
Thyroid		1	1	1	1	1	1	1		1	1		1	1	1		1
focal/multifocal mononuclear infiltrate									3								
focal inflammatory infiltrate												2					
ectopic thymic tissue																x	
Parathyroid		-	-	1	1	1	1	1	1	1	-	1	-	1	1	-	-
Adrenal		1	1		1	1	1	1		1	1	1	1	1	1	1	1
focal mononuclear infiltrate				2					2								

Code: x - condition present
1 - not remarkable
2 - very slight
3 - slight
4 - moderate
5 - marked
6 - extreme
- = not available

TABLE 13. Cont. Histomorphologic Observations.

Tissue Lesion	Group, Rabbit Number	Control								2500 mg/kg/day							
	Sex	M	M	M	M	F	F	F	F	M	M	M	M	F	F	F	F
		31609	31611	31615	31651	31616	31626	31640	31652	31629	31631	31633	31649	31612	31618	31632	31642
Lung																	
focal/multifocal peribronchial lymphoid hyperplasia		2						3	2	3		2	2	2	2	3	2
focal bronchial epithelial hyperplasia		2		2													
congestion		3	3	3		3					4		2	3			
interstitial pneumonia		2	2		3	3		3	3	3				2			2
focal/multifocal perivascular mononuclear infiltrate			3										2	2			
hemorrhage			2														
alveolitis			2	3			2	2					2				
multifocal accumulations of mononuclear cells (macrophages; lymphocytes)				2	3				2	3							3
edema						4					2						
focal pleural fibrosis						2											2
pleuritis									2								
focal perivascular inflammatory infiltrate									2								
focal peribronchiolitis											2					3	
focal accumulation of macrophages containing brown pigment												3					
focal subacute pneumonia													3				
focal vascularized fibrous pleural adhesions																x	
encapsulated abscess																x	
Trachea			1											1			
focal/multifocal mononuclear infiltrate - lamina propria		2		3	2	2	2	3			2	2	2		2	2	2
edema - lamina propria				2	2												
focal lymphoid hyperplasia - lamina propria								3									
trachea epithelial hyperplasia									3								
inflammatory infiltrate - lamina propria									4								
focal ulcerative tracheitis										3							
Heart			1	1	1		1				1	1		1		1	
focal vacuolation myocardial fibers		2							2								
focal mononuclear infiltrate - myocardium						2		2	2				3		2		2
focal mononuclear infiltrate - epicardium										2							
Spleen		1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Mesenteric Lymph Node		1		1	1	1				1	1	1		1	1	-	1
erythrophagocytosis			2				2		2								
sinusoidal inflammatory infiltrate								3									
edema													2				
microgranuloma													x				
Thymus		1	-	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Bone Marrow		1	1	1	1	1	1	1	1	1	1	1	1	1		1	1
focal osteoclastic resorption - bone															x		

Code: x - condition present; 1 - not remarkable; 2 - very slight; 3 - slight; 4 - moderate; 5 - marked; 6 - extreme; - - not available

3P-4A: Three Week Dermal Toxicity Study in Rabbits.

TABLE 13. Cont. Histomorphologic Observations.

Tissue Lesion	Control								2500 mg/kg/day							
Group, Rabbit Number	31609	31611	31615	31651	31616	31626	31640	31652	31629	31631	31633	31649	31612	31618	31632	31642
Sex	M	M	M	M	F	F	F	F	M	M	M	M	F	F	F	F
Stomach	1	1		1			1			1	1					
focal/multifocal mononuclear aggregates - lamina propria			3		2	2		2	2			2		2	3	2
focal/multifocal inflammatory infiltrate - submucosa			3					2						3		2
focal mucosal fibrosis			3													
focal serositis			2													
focal/multifocal inflammatory infiltrate - lamina propria					2			2								
focal perivascular mononuclear infiltrate - submucosa													2			
focal/multifocal inflammatory infiltrate - tunica muscularis																3
Small Intestine							1		1							1
subacute enteritis	2	4	3	5	2	4				5	2	2	4	3	2	
focal submucosal acute inflammatory infiltrate								2								
coccidiosis													x			
focal lymphoid necrosis - submucosal lymphoid follicles											x					
Large Intestine	1		1		1		1									
subacute typhlitis		3		3		4				4	3		4	3		2
subacute colitis				3						4						
nematode parasite in lumen				x					x			x	x		x	x
acute typhlitis								2							3	
acute colitis														2		
degenerative ova in cecal mucosa (coccidia)											x					
Pancreas	1	1	1	1	1	1	1	1	1		1	1	1	1	1	1
focal interstitial mononuclear infiltrate										2						
Liver																
focal/multifocal periportal mononuclear infiltrate	3	2	2		2		2	2	3		2				2	
peripheral hepatocellular vacuolation		2														
portal fibrosis		2	2	2	3	2	3	3				2	3		3	3
granulomatous foci			x									x				
bile duct proliferation				2	2	2		2							2	
focal/multifocal parenchymal inflammatory infiltrate				2					3		2	3		2		
centrolobular hepatocellular vacuolation								4								
aggregates of histiocytic and heterophilic cells in lumen of portal veins										x						
focal/multifocal portal inflammatory infiltrate												3				
Gallbladder	1		1	1	1		1	1	1	1	1	-	1	1	1	
edema - lamina propria		4				2										2
Kidney	1		1	1	1	1					1				1	1
organized thrombus-medulla		x														
focal/multifocal vacuolation - tubular epithelial cells							2	3	4	2		2	2			
focal fibrosis							2									
tubular atrophy							2									
focal tubular hyperplasia								2	3							
focal mineralization									3							
focal mononuclear infiltrate														2		

Code: x - condition present; 1 - not remarkable; 2 - very slight; 3 - slight; 4 - moderate; 5 - marked; 6 - extreme; - = not available

3P-4A: Three Week Dermal Toxicity Study in Rabbits.

TABLE 13. Cont. Histomorphologic Observations.

Tissue Lesion	Group, Sex	Control								2500 mg/kg/day							
	Rabbit Number	M 31609	M 31611	M 31615	M 31651	F 31616	F 31626	F 31640	F 31652	M 31629	M 31631	M 31633	M 31649	F 31612	F 31618	F 31632	F 31642
Urinary Bladder		1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Testes		1	1	1	1					1	1	1	1				
Ovaries corpora lutea						1	1	1	1					1	1	x	1
Prostate		1	-	1	1					1	1	1	-				
Uterus						1	1	1	1					1	1	1	1
Muscle		1	1	1	1	1	1	1		1	1		1	1	1	1	1
focal proliferation of sarcolemmal cells									3								
hemosiderin like pigment in macrophages												x					
Miscellaneous																	
Skin - Lateral Cervical Region																	
dermal and subcutaneous hemorrhage and edema with acute inflammatory infiltrate									3								

Code: x - condition present; 1 - not remarkable; 2 - very slight; 3 - slight; 4 - moderate; 5 - marked; 6 - extreme; - = not available